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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MUHAMMAD ASHRAF and ERIC J. BENJAMIN

Appeal 2009-001117
Application 10/663,506
Technology Center 1600

Decided: September 4, 2009

Before DEMETRA J. MILLS, LORA M. GREEN, and
MELANIE L. McCOLLUM, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1-6 and 10-20. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

Claim 1 is representative of the claim(s) on appeal, and read as follows:

1. A solid pharmaceutical composition for oral administration comprising a granulation, said granulation comprising

rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid,

a water soluble polymer in an amount of about 1 % to about 40% (wt/wt),

a surfactant in an amount of about 1 % to about 8% (wt/wt), an antioxidant from 0.001% to 3% (wt/wt), and a pH modifying agent.

The Examiner relies on the following evidence:

Azrolan	US 2002/0013335 A1	Jan. 31, 2002
Haeberlin	GB 2 327 611 A	Feb. 3, 1999

Madhavi et al., Hindered Phenols, Food Antioxidants: Technological, Toxicological and Health Perspectives, pp. 277-293 (1996).

The following grounds of rejection are before us for review:

I. Claims 1-6 and 10-20 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Azrolan, Haeberlin, and Madhavi;

II. Claims 1, 2-6, and 20 stand rejected on the ground of nonstatutory double patenting as being unpatentable over claims 55, 58-61, 65, 72, and 73 of copending U.S.S.N. 10/930,487 (now U.S. Pat. No. 7,271,177) as combined with Azrolan;

III. Claims 1, 2-6, and 20 stand provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 7, 8, and 11 of copending U.S.S.N. 11/030,685 as combined with Azrolan; and

IV. Claims 1, 2, 4, and 6 stand provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 12-16 and 19 of copending U.S.S.N. 10/626,943.

We affirm rejection II, but reverse the remaining rejections.

ISSUE (Obviousness)

The Examiner concludes that claims 1-6 and 10-20 are rendered obvious by the combination of Azrolan, Haeberlin, and Madhavi.

Appellants contend that nothing in the cited documents suggests the combination of excipients provided by the present formulation, and that the claimed percentages of ingredients are not provided by the references.

Thus, the issue on appeal is: Have Appellants demonstrated that the Examiner failed to set forth a prima facie case of obviousness?

FINDINGS OF FACT

FF1 The Examiner rejects claims 1-6 and 10-20 under 35 U.S.C. § 103(a) as being obvious over the combination of Azrolan, Haeberlin, and Madhavi (Ans. 3).

FF2 The Examiner cites Azrolan for teaching oral formulations of 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (*id.*).

FF3 The Examiner finds that Azrolan teaches a composition useful for tablet formation that include sodium lauryl sulfate, polyvinylpyrrolidone (PVP), poloxamer 188, sodium dodecyl sulfate, sodium citrate, and a dry granulation (*id.* at 3-4 (citing Azrolan, p. 2)). The Examiner further finds that Azrolan teaches other formulations, such as suspensions as a free base or sterile powders (Ans. 4).

FF4 The Examiner finds further that Azrolan teaches that "[u]nder ordinary conditions of storage and use, the preparation contains a preservative to prevent the growth of microorganisms." (*Id.* (citing Azrolan, p. 4).)

FF5 Azrolan is drawn to "the use of a rapamycin in the treatment and inhibition of cardiovascular disease, cerebral vascular disease, and peripheral vascular disease." (Azrolan, ¶2.)

FF6 Specifically, Azrolan teaches:

> Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia

> gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Preferred surface modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium stearate, cetostearl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine. It is more preferred that poloxamer 188 is used as the surface modifying agent. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). Preferred oral formulations of rapamycins are disclosed in U.S. Pat. Nos. 5,559,121; 5,536,729; 5,989,591; and 5,985,325, which are hereby incorporated by reference.

(*Id.* at ¶26.)

FF7 The Examiner notes that Azrolan does not teach the ranges of water soluble polymer, surfactant, and antioxidant that are used (Ans. 4).

FF8 As to claims 13 and 18, the Examiner notes that Arzolan does not teach the use of butylated hydroxyanisole (BHA) or butylated hydroxytoluene (BHT) (*id.*).

FF9 The Examiner cites Haeberlin for teaching the use of a carboxylic acid, such as malonic acid, oxalic acid, citric acid, and lactic acid, to stabilize (preserve) oral and parental formulations of macrolides, with rapamycin being preferred (*id.* at 5).

FF10 The Examiner finds further that the amount of citric acid used by Haeberlin is about 0.05 to 5% (*id.*).

FF11 The Examiner relies on Madhavi for teaching the use of BHA and BHT as the antioxidant, as required by claims 13 and 18 (*id.*).

FF12 The Examiner finds that Madhavi teaches that BHA may be the most widely used antioxidant in the food industry, and that BHT is also widely used (*id.*).

FF13 The Examiner notes that Madhavi teaches that BHA is rapidly absorbed in the gastrointestinal tract, is rapidly metabolized, and excreted (*id.*).

FF14 The Examiner notes further that Madhavi teaches that BHT is often used with other antioxidants, such as BHA, propyl galate, and citric acid (*id.*).

FF15 The Examiner concludes that it would have been obvious to the ordinary artisan at the time of invention to use PVP and sodium lauryl sulfate in a rapamycin composition because Azrolan "teaches that these components are useful for making tablets . . ., suspensions . . ., and sterile powders." (*Id.* at 8.)

FF16 The Examiner concludes further that it would have also been obvious "to formulate a composition of Azrolan . . . and citric acid because Haeberlin . . . teaches the use of various carboxylic acids to stabilize (i.e. preserve) oral and parenteral formulations of macrolides, preferably a rapamycin." (*Id.* at 7.)

FF17 Finally, the Examiner concludes that it would have been obvious "to formulate a composition of Azrolan . . . and the specific antioxidant [BHA] or [BHT] because Madhavi . . . teaches that BHA and BHT are extensively used antioxidants . . . ." (*Id.*)

PRINCIPLES OF LAW

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

While the analysis under 35 U.S.C. § 103 allows flexibility in determining whether a claimed invention would have been obvious, *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007), it still requires showing that "there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *Id.* "We must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention." *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008).

ANALYSIS

Azrolan, Appellants assert, is drawn to methods of treating cardiovascular disease with a rapamycin, which may include CCI-779, and also provides general information regarding excipients (App. Br. 11). Appellants assert that Haeberlin "provides for stabilization of macrolides, including rapamycins generally, by formulation with an acid such as malonic acid." (*Id.*) Madhavi, Appellants argue, is drawn to the use of BHA and BHT in the food industry (*id.*). Appellants argue that "nothing in the cited documents suggests the combination of excipients provided by the present

formulation, nor could the advantages thereof be predicted." (*Id.*) Appellants argue further that the claimed percentages of ingredients are not provided by the references, and that "it is the inventive selection of components and amounts of same in order to solve the problems identified by the Applicants that yielded the presently claimed compositions." (*Id.* at 11-12.)

We agree with Appellants. While Azrolan teaches that the rapamycin compositions may be formulated into tablets using wet granulation, it also teaches other formulations, and the wet granulation is just one of a list of formulations. In addition, while Azrolan may provide a list of excipients that may be used in the formulations, it is simply that, a list. Azrolan provides no guidance as to what excipients should be included in which formulations. Moreover, Azrolan provides no guidance as to what amounts of the excipients should be used in any of the listed formulations. The Examiner's reliance on Haeberlin and Madhavi do not remedy the deficiencies of Azrolan. The Examiner has thus failed to set forth a prima facie case of obviousness.

CONCLUSION OF LAW

We conclude that Appellants have demonstrated that the Examiner failed to set forth a prima facie case of obviousness.

We are thus compelled to reverse the rejection of claims 1-6 and 10-20 under 35 U.S.C. § 103(a) as being obvious over the combination of Azrolan, Haeberlin, and Madhavi.

ISSUE (Obviousness-Type Double Patenting)

The Examiner concludes that claims 1, 2-6, and 20 are unpatentable over claims 55, 58-61, 65, 72, and 73 of copending U.S.S.N. 10/930,487 (now U.S. Pat. No. 7,271,177) as combined with Azrolan; that claims 1, 2-6, and 20 are unpatentable over claims 1, 7, 8, and 11 of copending U.S.S.N. 11/030,685 as combined with Azrolan; and that claims 1, 2, 4, and 6 are unpatentable over claims 12-16 and 19 of copending U.S.S.N. 10/626,943.

Appellants contend that the Examiner has not set forth a reason as to why the instant claims are unpatentable over the cited patent and copending applications.

Thus, the issue on Appeal is: Has Appellants demonstrated that the Examiner erred in concluding that the pending claims are unpatentable over claims of the cited patent and copending applications?

ADDITIONAL FINDINGS OF FACT

FF18 The Examiner rejects[1] claims 1, 2-6, and 20 on the ground of nonstatutory double patenting as being unpatentable over claims 55, 58-61, 65, 72, and 73 of copending U.S.S.N. 10/930,487 (now U.S. Pat. No. 7,271,177) as combined with Azrolan (Ans. 8). As Appellants do not argue the claims separately, we focus our analysis on claim 1, and claims 2-6 and 20 stand or fall with that claim. 37 C.F.R. § 41.37(c)(1)(vii).

FF19 The Examiner finds that U.S.S.N. 10/930,487 claims a composition comprising an amorphous form of rapamycin (Ans. 9).

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[1] While the Answer refers to this rejection as being "provisional," it is no longer provisional as the copending application has been patented.

FF20 U.S.S.N. 10/930,487, now U.S. Pat. No. 7,271,177, claims:

> 27. A pharmaceutical composition comprising an amorphous form of rapamycin 42-ester with 3-hydroxy-2-(hydroxymethy1)-2-methylpropionic acid, comprising:
>
> (i) an amorphous form of rapamycin 42-ester with 3-hydroxy-2-(hydroxymethy1)-2-methylpropionic acid according to claim 1, (ii) a metal chelator, (iii) a pH adjuster, (iv) a surfactant, (v) at least one filler, (vi) a binder, (vii) a disintegrant, and (viii) a lubricant.
>
> 30. The pharmaceutical composition according to claim 27, wherein said pH adjuster comprises citric acid, ascorbic acid, fumaric acid, or malic acid.
>
> 31. The pharmaceutical composition according to claim 30, wherein said pH adjuster is citric acid.
>
> 32. The pharmaceutical composition according to claim 30, wherein said surfactant is selected from a polysorbate, a sorbitan ester, poloxamer, or sodium lauryl sulfate.
>
> 33. The pharmaceutical composition according to claim 32, wherein said surfactant is sodium lauryl sulfate.
>
> 37. The pharmaceutical composition according to claim 27, wherein said binder comprises povidone, hydroxypropylmethylcellulose, carboxyrnethylcellulose, or gelatin.
>
> 44. The pharmaceutical composition according to claim 27, wherein said components are dry granulated and compressed into a form suitable for administration to a mammalian subject.
>
> 45. The pharmaceutical composition according to claim 27, wherein said components are dry granulated and compressed into a form suitable for administration to a mammalian subject.

(App. Br. 13-14.)

FF21 The Examiner notes that the claims do not specify the amount of antioxidant, the amount of water soluble polymer, and the amount of surfactant (Ans. 9).

FF22 The Examiner notes further that the above claims do not specify the use of polyvinylpyrrolidone (PVP) (*id.*).

FF23 Azrolan is relied upon for teaching oral formulations of 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid which may include PVP (*id.* at 9-10).

FF24 The Examiner concludes that it would have been obvious to formulate a pharmaceutical composition comprising a water soluble polymer and an antioxidant because hydroxypropylmethylcellulose (claim 37) is a water soluble polymer, and ascorbic acid (claim 30) is an antioxidant (*id.* at 10).

FF25 The Examiner provisionally rejects claims 1, 2-6, and 20 on the ground of nonstatutory double patenting as being unpatentable over claims 1, 7, 8, and 11 of copending U.S.S.N. 11/030,685 as combined with Azrolan (Ans. 11).

FF26 The Examiner relies on U.S.S.N. 11/030,685 for teaching a composition comprising micronized CCI-779 (Ans. 11).

FF27 The claims of U.S.S.N. 11/030,685 relied upon by the Examiner are set forth below:

> 1. A pharmaceutical composition comprising micronized CCI-779.
>
> 7. The pharmaceutical composition according to claim 1, further comprising:
> about 5% w/w to about 6/5% w/w surfactant;

about 80% w/w to about 85% w/w filler/binder;
about 4% w/w to about 6% w/w disintegrant.

8. The pharmaceutical composition according to claim 7, wherein the surfactant is sodium lauryl sulfate.

11. The pharmaceutical composition according to claim 1, further comprising one or more antioxidants, a chelating agent and/or a pH modifier.

(App. Br. 16.)

FF28 The Examiner notes that the 11/030,685 application does not claim a composition comprising a granulation (Ans. 12).

FF29 The Examiner finds, citing claim 27 of the application (not relied upon in the statement of the rejection), that "the composition is in granular form due to formation of a tablet." (*Id.*)

FF30 Azrolan is relied upon for teaching oral formulations of 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid which may include PVP (*id.* at 12-13).

FF31 The Examiner provisionally rejects claims 1, 2, 4, and 6 on the ground of nonstatutory double patenting as being unpatentable over claims 12-16 and 19 of copending U.S.S.N. 10/626,943 (Ans. 13).

FF32 The Examiner finds that the claims of U.S.S.N. 10/626,943 teach a parenteral formulation (*id.* at 14).

FF33 The claims of U.S.S.N. 10/626,943 relied upon are set forth below:

12. A parenteral formulation which comprises CCI-779, an alcoholic solvent, an antioxidant, a diluent solvent, and a surfactant.

> 13. The formulation according to claim 12, wherein the alcoholic solvent is ethanol, propylene glycol, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 600, or polyethylene glycol 1000.
>
> 14. The formulation according to claim 12, wherein the antioxidant is citric acid, glycine, d, 1-a-tocopherol, BHA, BHT, monothoglycerol, ascorbic acid, or propyl gallate.
>
> 15. The formulation according to claim 12, wherein the diluent solvent is water, ethanol, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 600, polyethylene glycol 1000, or propylene glycol.
>
> 16. The formulation according to claim 12, wherein the surfactant is polysorbate 20, polysorbate 80, a bile acid, lecithin, an ethoxylated vegetable oil, vitamin E, or polyoxyethylene-polyoxyproylene block copolymers.
>
> 19. The formulation according to claim 12, wherein the formulation comprises a concentration of antioxidant from about 0.0005 to 0.5% w/v.

(App. Br. 19.)

FF34 The Examiner concludes that "[o]ne having ordinary skill in the art would find it obvious to formulate a pharmaceutical composition comprising a solid granulation because it is a species of the genus parental formulation (see claim 12)," that is "a parental formulation can be in a solid granulation." (Ans. 15.)

PRINCIPLES OF LAW

The key question in any obviousness double patenting analysis is: "Does any claim in the application define merely an obvious variation of an

invention claimed in the patent asserted as supporting double patenting?" *General Foods Corp. v. Studiengesellschaft Kohle mbH,* 972 F.2d 1272, 1278 (Fed. Cir. 1992) (discussing *In re Vogel,* 422 F.2d 438 (CCPA 1970)). As stated by our reviewing court in *In re Braat,* 937 F.2d 589, 592-93 (Fed. Cir. 1991) (citation omitted):

> Obviousness-type double patenting is a judicially created doctrine intended to prevent *improper* timewise extension of the patent right by prohibiting the issuance of claims in a second patent which are not "patentably distinct" from the claims of a first patent.

An analysis analogous to an obviousness analysis under 35 U.S.C. § 103(a) comes into play during the step of determining the obviousness of the "difference" between the claimed invention and the patented invention. *See Studiengesellschaft Kohle mbH v. N. Petrochemical Co.,* 784 F.2d 351, 355 (Fed. Cir. 1986); *In re Longi,* 759 F.2d 887, 892-93 (Fed. Cir. 1985). The patent's Specification may be used as a dictionary to determine the meaning of terms in the patent's claim. *In re Vogel,* 422 F.2d at 441. Moreover, if a claim in a patent application is generic to the subject matter of a claim in a co-owned issued patent, the claim in the patent application is subject to rejection for obviousness-type double patenting unless a terminal disclaimer is filed. *See In re Goodman,* 11 F.3d 1046, 1053 (Fed. Cir. 1993).

ANALYSIS

Appellants argue as to the rejection over the U.S.S.N. 10/930,487, now U.S. Pat. No. 7,271,177, that the Examiner has only provided a

conclusory statement of obviousness, and one would not combine Azrolan with the claims of the '177 patent as Azrolan is drawn to a method of treating cardiovascular disease (App. Br. 14). Appellants also argue that the '177 contains additional components not required by the pending claims (*id.*). Appellants argue further that Azrolan is drawn to treating cardiovascular disease, and one would not combine Azrolan with the claims of the '177 patent to arrive at the instant claims.

Appellants' arguments have been considered, but are not found to be convincing. The Examiner has explained why it would have been obvious to arrive at a composition as set forth by instant claim 1 (FF24). In addition, as claim 1 uses the transitional phrase "comprising," it does not exclude additional components, such as a metal chelator.

As to Azrolan, its teachings are not required for claim 1, but for claim 2, 3 and 19, which specify that the water soluble polymer is PVP. Unlike the obviousness rejection analyzed above, the claims of the '771 patent set forth a composition that is generic to the claimed composition, and given the claims of the '771 patent and the teaching of Azrolan, the ordinary artisan would have understood that PVP could be substituted for hydroxypropylmethylcellulose. Thus, Appellants have failed to demonstrate that the obviousness-type double-patenting rejection is in error.

Appellants argue as to the rejection over the U.S.S.N. 11/030,685, that the use of the term "tablet" in claim 27 does not imply that the composition is in granular form (App. Br. 18).

In this instance, we find that Appellants have the better argument. The Examiner has provided no evidence or scientific reasoning why a tablet necessarily requires a granular form.

Appellants argue as to the rejection over U.S.S.N. 10/626,943, that a parenteral formulation is administered by injection, and thus the "'943 application's claims to *parenteral* formulations would not lead one of ordinary skill in the art to prepare *solid* pharmaceutical compositions for *oral* administration." (App. Br. 20.)

Again, we find that Appellants have the better argument. The Examiner has provided no evidence or scientific reasoning why a granulation (a solid form) is a species of a parental (liquid) form.

CONCLUSIONS OF LAW

We thus conclude that Appellants have demonstrated that the Examiner erred in concluding that the pending claims are unpatentable over the claims of copending applications 11/030,685 and 10/626,943, but have not demonstrated that the Examiner in concluding that the pending claims are unpatentable over the claims of U.S.S.N. 10/930,487, now U.S. Pat. No. 7,271,177.

We thus affirm the rejection of

claims 1, 2-6, and 20 on the ground of nonstatutory double patenting as being unpatentable over claims 55, 58-61, 65, 72, and 73 of copending U.S.S.N. 10/930,487 (now U.S. Pat. No. 7,271,177) as combined with Azrolan;

but reverse the provisional rejections of

claims 1, 2-6, and 20 on the ground of nonstatutory double patenting as being unpatentable over claims 1, 7, 8, and 11 of copending U.S.S.N. 11/030,685 as combined with Azrolan; and

claims 1, 2, 4, and 6 on the ground of nonstatutory double patenting as being unpatentable over claims 12-16 and 19 of copending U.S.S.N. 10/626,943.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART

cdc

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